National Institute on Aging

VIRTUAL WORKSHOP- April 7-8, 2022

UNDERSTANDING HETEROGENEITY OF RESPONSES TO, AND OPTIMIZING CLINICAL EFFICACY OF, EXERCISE TRAINING IN OLDER ADULTS

WORKSHOP PROGRAM

TABLE OF CONTENTS

National Institute on Aging (NIA), National Institutes of Health (NIH)
VIRTUAL WORKSHOP
April 7- 8, 2022

UNDERSTANDING HETEROGENEITY OF RESPONSES TO, AND OPTIMIZING CLINICAL EFFICACY OF, EXERCISE TRAINING IN OLDER ADULTS

SPEAKERS' BIOGRAPHIES

Jacob Allen, Ph.D., University of Illinois
Dr. Allen's research program concentrates on understanding how specific environmental interventions and conditions—exercise, aging, stress, and nutrition—interact to influence gut microbial communities (i.e., gut microbiota) during both homeostatic and pathological disease states. Dr. Allen's lab applies research methods spanning in vitro organoid systems, pre-clinical animal models, and human studies. The lab is particularly interested in understanding how gut microbes interact with the immune system to shape human physiology.

Daniel P. Beavers, Ph.D., Wake Forest School of Medicine
Dr. Daniel P. Beavers is an Associate Professor of Biostatistics and Data Science within the Division of Public Health Sciences at the Wake Forest School of Medicine. His work broadly encompasses the treatment effect of lifestyle-based interventions including weight loss and exercise among older adults, particularly as a means to improve physical function and to reduce the impact of aging- and obesity-related disease. He is the recipient of an NIA grant (R21 AG061344) exploring physical function response heterogeneity of among older adults undergoing weight loss with or without exercise across 8 pooled randomized controlled trials.

Thomas Buford, Ph.D., F.A.C.S.M., F.A.H.A., University of Alabama at Birmingham
Dr. Buford's research interests have long focused on methods to improve the clinical efficacy of exercise among older adults, with particular emphasis on the improvement of physical function and prevention of disability. Modulation of the renin-angiotensin system and the impact of antihypertensive drugs on functional responses to exercise has been one key area of his research for the past decade.

Linda Collins, Ph.D., New York University
Dr. Collins's interests are focused on development, dissemination, and application of the multiphase optimization strategy (MOST), an innovative methodological framework for optimizing and evaluating interventions in public health, education, criminal justice, and many other fields. Dr. Collins has collaborated on research applying MOST in a range of areas, including HIV, smoking cessation, prevention of excessive alcohol use in college students, and weight loss. She is also collaborating on development of methods for decision-making based on the results of an optimization trial; optimizing interventions for cost-effectiveness; and optimizing adaptive interventions. Her research has been funded by the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, the National Cancer Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National

Science Foundation. Dr. Collins's publications have appeared in journals in the behavioral sciences, quantitative methodology, medicine, and engineering.

Karina Davidson, Ph.D., Northwell Health
Karina Davidson, Ph.D., is Dean of Academic Affairs, Director of the Institute of Health System Science at the Feinstein Institutes for Medical Research, Endowed Donald and Barbara Zucker Professor in Health Outcomes at the Zucker School of Medicine and Senior Vice President, Research at Northwell Health. Dr. Davidson's research focuses on innovations in personalized trials and healthcare systems to manage chronic disease and patient symptoms that incorporate patient preferences and values. Dr. Davidson was awarded the NIH Transformative R01 grant to accomplish the vision of reimagining the process by which therapies are tested in the clinical encounter, with the goal of identifying therapies that will provide maximal benefit and minimal harm for each individual patient., with the use of Personalized (N of 1) trials.

Kirk Erickson, Ph.D., University of Pittsburgh
Dr. Kirk Erickson is the Director and Principal Investigator of the Brain Aging and Cognitive Health Laboratory at the University of Pittsburgh and Center for the Neural Basis of Cognition. He was a member of the 2018 Physical Activity Guidelines Advisory Committee, and chair of the Brain Health subcommittee charged with developing the second edition of the Physical Activity Guidelines for Americans. Dr. Erickson conducts observational studies and randomized clinical trials aimed at understanding the effects of exercise behaviors on brain health across the lifespan and various health conditions. This research has resulted in > 250 articles and 15 book chapters. Much of his work has emphasized the need to better understand heterogeneity of response and the underlying mediators of exercise on neurocognitive health.

Karyn A. Esser, Ph.D., University of Florida Health
Dr. Esser is Professor of Physiology and Functional Genomics and Associate Director of the Myology Institute at the University of Florida. Her lab has been working in the area of skeletal muscle adaptation for over 20 years. Initially her research was focused on understanding the molecular mechanisms that underly adult skeletal muscle adaptation to exercise. However, in 2002, she "accidently" discovered that genes important for circadian rhythms were also at work in skeletal muscle. Since then, Dr. Esser's lab has pioneered research on the role of circadian rhythms and the molecular clock mechanism in skeletal muscle. Her lab has demonstrated that the muscle circadian clock is necessary for maintaining healthy metabolism and muscle strength. Her lab is currently focused on; 1) basic science experiments to define the molecular network downstream of the clock that modulates muscle health. 2) learning how age changes the clock function in skeletal muscle and other tissues; and 3) learning how exercise works with the circadian clock to hellp promote tissue and systemic health.

Bret H. Goodpaster, Ph.D., AdventHealth
Bret Goodpaster, Ph.D. is a Senior Investigator and Scientific Director at the AdventHealth Translational Research Institute (TRI). Dr. Goodpaster's primary research is in the pathophysiology of human obesity, insulin resistance, and diabetes, and to help decipher biological mechanisms underlying the health benefits of exercise. He has received a number of awards and honors for his work, including the Nathan Shock Award from the National Institute of Aging in 2008, for his work investigating the role of muscle fat infiltration in aging and

muscle quality. He is particularly well known for "the athlete's paradox" which has shifted the paradigm in Type 2 diabetes research to investigate, how and why does fat accumulation in muscle cause insulin resistance in some subjects but not others?

Matthijs K.C. Hesselink, Ph.D., Maastricht University
Dr Matthijs Hesselink is professor in physical activity and metabolic health at Maastricht University, the Netherlands. He is particularly interested in translational studies towards the role of myocellular lipid droplets and mitochondrial network remodeling in insulin sensitivity. Optimizing the health benefits of exercise training e.g., by appropriate timing of training sessions and reducing exercise response heterogeneity, is amongst his recent interests.

Eric Laber, Ph.D., Duke University
Eric Laber is Professor of Statistical Science and Professor of Biostatistics and Bioinformatics at Duke University. His research focuses on methods development for data-driven decision making with applications in precision public health, defense, sports/e-sports, and inventory management. He is also passionate about K-12 STEM Outreach (www.laber-labs.com).

Nathan K. LeBrasseur, Ph.D., M.S., Mayo Clinic
Nathan LeBrasseur, P.T., Ph.D., is a Professor and the Co-Chair of Research in the Department of Physical Medicine and Rehabilitation at Mayo Clinic. Dr. LeBrasseur is Co-Director of the Paul F. Glenn Center for Biology of Aging Research at Mayo Clinic and serves as the Scientific Director of the Office of Translation to Practice. His laboratory conducts translational "bench-to-bedside" research on strategies to improve physical function, metabolism, and resilience in the face of aging and disease. His latest work has centered on cellular senescence, a biological mechanism that underlies aging, and interventions to counter this process and, in turn, optimize later life health and function. Dr. LeBrasseur has received the Glenn Award for Research in Biological Mechanisms of Aging, the Nathan W. Shock Award from the National Institute on Aging, and the Vincent Cristofalo Rising Star Award in Aging Research from the American Federation for Aging Research. He is the current chair of the Cellular Mechanisms in Aging and Development Study Section.

Kerrie Moreau, Ph.D., University of Colorado Anschutz Medical Campus
Dr. Moreau's is a Professor in the Department of Medicine, Division of Geriatric Medicine and Director of the Cardiovascular BioImaging Core at the University of Colorado Denver Anschutz Medical Campus and a Research Health Scientist in the Geriatric Research Education Clinical Center (GRECC), Denver Veterans Administration Medical Center, Denver, CO. Her research evaluates the intersection of chronological and gonadal aging on cardiovascular function. Her work has evaluated mechanisms by which changes in gonadal function and sex hormones in women (menopause), men (andropause) and gender-affirming hormone therapy (transgender health) alter cardiovascular aging. As an exercise physiologist, she also investigates the modulatory influence of sex/gender and sex hormones on cardiovascular adaptations to habitual exercise. Recently, Dr. Moreau has expanded her work to evaluate the effects sex hormones on cerebrovascular function and brain aging.

Charlotte A. Peterson, Ph.D., University of Kentucky
Dr. Peterson is the Joseph Hamburg Endowed Professor and Director of the Center for Muscle Biology at the University of Kentucky. She served as Associate Dean for Research from 2006-2016, and then served as a scientific officer for the NIH initiative entitled "Molecular Transducers of Physical Activity Consortium" (MoTrPAC) from 2016-2018. Dr. Peterson received her Ph.D. from the University of Virginia in 1985 followed by two postdoctoral fellowships, at the National Eye Institute and Stanford University School of Medicine, where her interest in skeletal muscle research began. She served on the faculty at the University of Arkansas for Medical Sciences from 1990-2006. Dr. Peterson's research focuses on elucidation of cellular and molecular mechanisms controlling skeletal muscle structure and function and adaptation to exercise. Her long-term goal is to develop new strategies to prevent frailty and loss of functional independence in older persons. Dr. Peterson is a Fellow of the Gerontological Society of America and was recently appointed to the National Advisory Council on Aging.

Courtney M. Peterson, Ph.D., University of Alabama at Birmingham
Dr. Courtney M. Peterson is an Associate Professor at the University of Alabama at Birmingham. She is internationally recognized for her research on a type of intermittent fasting called time-restricted eating (TRE). She has been involved in 10 clinical trials on TRE—spanning type 2 diabetes, obesity, aging, and cancer—including seven as the PI or site PI. The goal of her research is to develop novel dietary interventions involving intermittent fasting, chronobiology, and diet quality to treat cardiometabolic diseases.

Jane E. Reusch, M.D., University of Colorado Anschutz Medical Campus
A physician-scientist, Dr. Reusch has made fundamental contributions to our understanding of the cellular metabolism of diabetes and its complications. The focus of her basic science program is to identify the cellular and molecular mechanisms (i.e., mitochondrial dysfunction and vascular inflexibility) that contribute to cardiac, vascular, and skeletal muscle dysfunction in diabetes. Her shared clinical translational research program with Drs Judy Regensteiner and Kristen Nadeau examines and targets the biological variables in people with diabetes, particularly women, that lead to decreased functional exercise capacity, insulin resistance and shortened lifespan.

Lauren M. Sparks, Ph.D. AdventHealth
Dr. Lauren M. Sparks is an Associate Investigator at the AdventHealth Translational Research Institute in Orlando, Florida. Dr. Sparks pursues translational investigations on the epigenomic regulation of exercise response variation in clinical outcomes relevant to metabolic disease and aging. She aims to advance the field of exercise and type 2 diabetes and potentially shift the paradigm, allowing interventions to be targeted to those individuals most likely to benefit as well as identify novel approaches to treat those who do not. Dr. Sparks also investigates the bi-directional communication between muscle and adipose tissues in obesity and aging. Prior to joining the TRI, Dr. Sparks was a postdoctoral fellow at Maastricht University in the Netherlands. Dr. Sparks was born in Patterson, Louisiana. She earned a B.S. in Zoology and a B.A. in Spanish in 2002 and continued on to earn her Ph.D. in Molecular Biology in 2006 from Louisiana State University while executing her dissertation work at Pennington Biomedical Research Center.

John P. Thyfault, Ph.D., F.A.C.S.M., F.T.O.S., University of Kansas Medical Center
Dr. John Thyfault has research expertise in metabolism, mitochondrial energetics, obesity, and exercise physiology using translational approaches in animal models and human subjects. The broad theme of his research program focuses on the mechanisms by which exercise, physical activity, and aerobic capacity reduce susceptibility for obesity, chronic metabolic disease states of insulin resistance and fatty liver, and neurometabolic deficits associated with aging.

Shawn D. Youngstedt, Ph.D., Arizona State University
Dr. Youngstedt is a Professor in the Edson College of Nursing and Health Innovation at Arizona State University, and is research scientist at the Phoenix VA. He is currently on sabbatical at the University of Arizona in Tucson. His research interests include the effect of exercise on sleep in health adults and individual with sleep disorders, the effects of bright light, exercise and melatonin on the circadian system, and the risks of long sleep and sleep extension. His work has been supported by NIH, the DoD, the VA, and the CDC.

Juleen Zierath, Ph.D., Karolinska Institutet
Juleen R. Zierath is a native of Milwaukee Wisconsin. She is Professor of Experimental Physiology at Karolinska Institutet, Stockholm, Sweden and Professor of Integrative Physiology and Executive Director at the Novo Nordisk Foundation Center for Basic Metabolic Research at University of Copenhagen, Denmark. She performs translational research to delineate mechanisms for the development of insulin resistance in Type 2 diabetes. Current work is focused on the role of epigenetic modifications in the development of insulin resistance and the interaction between circadian rhythms and exercise training in the control of metabolism. Zierath is a member of the Nobel Assembly and Nobel Committee for Physiology or Medicine. She is a Member of the Royal Swedish Academy of Science and Academia Europaea. She has previously been Chairman of the Nobel Committee, and is former President of the European Association for the Study of Diabetes. She is past Editor-in-Chief of Diabetologia and currently holds editorial positions with several scientific journals in the fields of endocrinology, metabolism, and interdisciplinary sciences. Professor Zierath has received the Claude Bernard Medal and Lectureship from the European Association for the Study of Diabetes, the Datta Lectureship Award for outstanding achievement from the Federation of European Biochemical Society, the Harold Rifkin Award for Distinguished International Service in the Cause of Diabetes, the Knud Lundbaek Award from the Scandinavian Society for the Study of Diabetes, J.B. Wolffe Memorial Lectureship Award from the American College of Sports Medicine, The Nordic Medicine Prize for Research in Diabetes, and a Distinguished Alumnus Award and Honorary Doctorate of Science from University of Wisconsin-River Falls.

ABSTRACTS

OVERVIEW

The Pillars of Aging and their Potential to Impact Adaptations to Exercise - The profound effects of exercise on delaying if not preventing numerous age-associated chronic diseases and geriatric syndromes strengthens the premise that exercise counters the fundamental biology aging. Indeed, there is unequivocal evidence that exercise promotes mitochondrial abundance and function, protein turnover, intercellular communication, and regenerative capacity, and, to some extent, its ability to counter inflammation, DNA damage, and cellular senescence. What is less clear is whether these recognized *pillars of aging* influence the responsiveness of older adults to exercise interventions and, in turn, account for the heterogeneity observed in the adaptations across multiple organs and physiological systems. This seminar will briefly overview the pillars of aging and the rationale for better understanding the interplay between the biology of aging and the exercise response.

Understanding the Biology of Exercise Response Variability - Exercise and physical activity confer many health benefits. Unfortunately, most people do not consistently engage in enough exercise or obtain adequate physical activity to realize these benefits. Even in those who do exercise, however, there is significant variability in their responses to exercise, and some may have a poor response to exercise. Although we understand some of the mechanisms underlying the health-promoting effects of exercise, there is much yet to learn about the biology of exercise response variation. How does the amount or dose, or type of exercise, e.g., aerobic or resistance exercise influence the response variability? The effects of intentional exercise on non-exercise physical activity are also important to consider in the context of exercise response variability. Does intentional exercise increase or decrease physical activity or sedentary behavior throughout the rest of the day? How does this physical activity, or lack of physical activity - sedentary behavior – influence biological and clinical outcomes? The NIH recently launched a large investigation in pre-clinical rodent studies and a human exercise trial, the Molecular Transducers of Physical Activity Consortium (MoTrPAC), to discover novel molecules underlying the health benefits of exercise and to better understand individual response variability to exercise. The MoTrPAC human studies, however, are limited to a healthy cohort, and phenotypic outcomes are narrow. Future studies are needed to rigorously interrogate the biology of exercise response variation employing well controlled trials in which exercise dose, clinically relevant outcomes and other non-exercise behaviors are quantified in both healthy and diseased populations. Then a better understanding of exercise responses variation will lead to improved precision medicine approaches to promote and prescribe tailored exercise programs better suited to individual goals and health benefits.

SESSION 1: IMPACT ON PHARMACOTHERAPY

Mechanisms Underlying Resistance Exercise Response Heterogeneity in Older Individuals Revealed by Drug-Exercise Interactions - Although progressive resistance training (PRT) is

the most effective way to maintain muscle mass and strength in older persons, the hypertrophic response is highly variable. Our work has demonstrated a close association of the change in alternatively activated, M2-like macrophages in muscle with the growth response to PRT. We undertook the MASTERS randomized, controlled clinical trial to test the hypothesis that adjuvant metformin would augment the PRT response in individuals >65 years of age by promoting accumulation of M2-like macrophages. Contrary to our hypothesis, metformin blunted the hypertrophic response with no significant effect on macrophage abundance. Surprisingly, those randomized to metformin who were also taking a prescribed statin showed a higher growth response than those on metformin alone associated with a higher increase in M2-like macrophages. Characterization of macrophage population heterogeneity in response to an acute bout of RT may identify new targets to improve training outcomes. Clinical trials focused on exercise-drug interactions should be undertaken to determine effects on exercise outcomes.

Impacts of Antihypertensive Drugs and Exercise on Late-Life Physical Function - To date, physical exercise is the only intervention consistently shown to improve physical function and prevent physical disability among older adults. However, older adults' functional responses to exercise are quite variable even when adherence to exercise is high. Pharmacotherapy, nearly ubiquitous among older adults, represents a key confounding factor in evaluating the impact of exercise on functional changes among older adults. Antihypertensive drugs are one of the most prevalent classes of pharmacologics used by older adults and have a variety of physiologic effects aside from maintaining blood pressure. This discussion will briefly cover knowledge on the impacts of antihypertensives on functional responses to exercise.

Statins and Exercise Interactions

More than 40 million Americans currently take statins for the treatment or prevention of hyperlipidemia and cardiovascular disease (CVD). Despite statins having a profound impact on lowering cardiovascular risk and disease, statins are not without risk. Complications include mild to moderate skeletal muscle adverse reactions, with reported incidence as high as 25%. In addition, statins have been shown to worsen insulin resistance and increase risk for type 2 diabetes. Disturbances in mitochondrial respiratory function have been implicated as a causal factor in these pathologies, but studies to test these potential links have not been conducted in human subjects undergoing statin therapy. Patients taking statins are also commonly advised to exercise regularly to further lower the risk for metabolic and cardiovascular disease. However, recent evidence suggests that statins can impair important exercise adaptations, and that this, again, may occur because of statins negatively impacting mitochondria in skeletal muscle. In summary, understanding how long-term statin therapy affects mitochondrial function in skeletal muscle is extremely important clinically, given the critical role skeletal muscle plays in maintaining metabolic and cardiovascular health. This presentation will discuss the evidence that statins can impair skeletal muscle and whole-body exercise adaptations. Factors that impact statin and exercise interactions will also be discussed including the timing of initiating exercise and statin therapy, the role of baseline mitochondrial function and aerobic fitness levels on susceptibility to statins deleterious effects, and the role of the liver in catabolizing statins.

SESSION 2: IMPACTS ON OUTCOMES

Sex Differences in Vascular Endothelial Adaptations to Exercise: Role of Gonadal Function and Sex Hormones - Vascular aging, featuring endothelial dysfunction, is a major risk factor for cardiovascular disease. Oxidative stress, characterized as excessive production of reactive oxygen species relative to antioxidant defense capacity, reduces nitric oxide (NO) bioavailability and impairs endothelial function. Exercise is promoted as a strategy to slow and reverse vascular aging and reduce cardiovascular disease risk. We and others have shown that endurance exercise attenuates or ameliorates the age-related endothelial dysfunction (both at the macro- and micro-vascular level) in healthy middle-age and older men by reducing oxidative stress and preserving NO bioavailability. Surprisingly, improvements in endothelial function with endurance exercise training are not consistently observed in postmenopausal women, suggesting sex-specific adaptive responses to endurance exercise in healthy middle-age and older adults. The reasons for this sex disparity are unclear but may be related to differences in gonadal status. Sex hormones (i.e., estrogen and testosterone) are potent modulators of vascular aging, and women have marked, relatively abrupt reductions in circulating estrogen with menopause, whereas a parallel change is not observed in men. We have shown that treating postmenopausal women with estrogen appears to restore the ability of endurance exercise to improve NO-mediated endothelial function by reducing oxidative stress, suggesting that estrogen can "recouple" endothelial adaptations to endurance exercise. Several gaps in knowledge exist in our understanding of potential sex differences in the beneficial effects of regular endurance exercise on age-associated endothelial dysfunction. More information is needed on the role of gonadal function and circulating sex hormones (i.e., estrogens and testosterone) in transducing the exercise training stimulus in both sexes. Additionally, because it is not practical to treat all postmenopausal women with estrogen-based hormone therapy to transduce the endurance exercise signal for endothelial adaptations, it is important to establish evidence-based alternative strategies that exert estrogen like effects for transducing the exercise signal for vascular adaptations in postmenopausal women. Finally, there are limited data on the mechanisms that mediate endothelial adaptations to endurance exercise with aging in women and men and additional studies are needed to establish whether there are sex differences in the mechanisms of action by which exercise enhances endothelial function. Addressing these gaps in knowledge will help inform the development of future sex-specific exercise guidelines and/or other therapies that are effective for cardiovascular disease prevention.

Diabetes and Cardiorespiratory Fitness: A Collision of Metabolic and Vascular Inflexibility - Cardiorespiratory fitness (CRF) represents a systems biology assay of the general health of an individual. This powerful assay is the strongest biological predictor of longevity in human subjects. Adults and youth with type 1 and type 2 diabetes, without established complications, have ~20% decrease in cardiorespiratory fitness. We seek to understand mechanisms underlying impaired CRF in people with diabetes. Our current working hypothesis is that diabetes alters perfusion/blood flow distribution to the heart and the skeletal muscle with resultant cardiac diastolic dysfunction and decreased skeletal muscle oxidative flux. We have coined this change in perfusion as "vascular inflexibility" which contributes to decreased CRF and may contribute to the metabolic inflexibility. This pathology is responsive to exercise and pharmacological intervention and differs in males and females with and without diabetes. Subclinical cardiac dysfunction is present in adults and youth with new onset diabetes. Right heart catheterization demonstrated exercise mediated increased pulmonary capillary wedge pressure (diastolic dysfunction) with impaired exercise mediated increases in myocardial perfusion in

premenopausal women with type 2 diabetes. People with diabetes have an increased perceived rate of exertion relative to VO2 peak. Women with type 2 diabetes demonstrate greater changes in diastolic parameters than men. Unpublished work in sedentary women and men with and without type 2 diabetes (CMR and echocardiography with strain) demonstrates decreased end systolic and diastolic volumes in people with diabetes compared to sedentary overweight controls which improve with four-month graded aerobic exercise training (only in the people with type 2 diabetes). Arterial stiffness is a potent predictor of cardiovascular outcomes impacting cardiac workload and end organ fluid dynamics. We observe increased central arterial stiffness and systemic arterial stiffness in adults and youth with uncomplicated diabetes. New data demonstrate significant increases in central arterial pressure, measured using 2D and 4D MRI, in sedentary obese and participants with and without type 2 diabetes compared to age matched lean controls. Arterial stiffness improves similarly in people with and without diabetes with exercise training. Skeletal muscle oxidative flux, as measured using MR spectroscopy, is decreased in sedentary individuals with type 1 and type 2 diabetes. Data are mixed on the impact of diabetes on mitochondrial respiration with muscle biopsy. In our cohort of 94 sedentary individuals with and without type 2 diabetes, we found no difference in muscle fiber oxygen consumption by diabetes status. Supplemental oxygen was employed to increase muscle oxygen tension in a subset of this population. Supplemental oxygen improved muscle oxidative flux only in people with type 2 diabetes. Single leg exercise training (SLET) led to improvements in muscle fiber respiration in all participants. With SLET in vivo mitochondrial oxidative flux improved in the people with type 2 diabetes and no longer differed from the overweight controls. Response to supplemental oxygen was no longer observed in the people with type 2 diabetes. These data suggest that exercise training improves muscle blood flow and is a modifiable target for skeletal muscle function in diabetes.

Exercise Response Variation in Type 2 Diabetes: A Clinical Outcome with Epigenomic Underpinnings - Exercise is beneficial for most individuals with obesity and metabolic diseases such as type 2 diabetes (T2D), but why some individuals do not respond favorably to exercise training is largely unexplored. Classic genetic studies demonstrated that the training response [change in VO2max] is largely heritable, suggesting that DNA sequence variation and/or epigenetic modification may influence “exercise response variation”. Moreover, DNA hypo-methylation is reported as an early event in contraction-induced gene activation in muscle, and prolonged exercise training modifies genome-wide DNA methylation in muscle. Recent studies have implicated a plethora of signaling mechanisms originating from mitochondria that modify the nuclear epigenome and vice-versa. We recently discovered that some individuals with T2D did not improve muscle mitochondrial capacity in vivo after exercise, and that these “Non-responders” also displayed a “non-response” in insulin sensitivity and glycemic control -- despite having a significant increase in VO2max. A distinct pre-training molecular pattern (DNA methylation, RNA expression) in skeletal muscle tissue from these same individuals predicted this “exercise non-response”. Our data suggest an interdependence between muscle mitochondrial capacity and insulin sensitivity in response to training, linking a molecular mechanism within skeletal muscle to a clinically relevant outcome, e.g. insulin sensitivity, in T2D. The term “Non-Responder” can have negative connotations; thus, we prefer to use the term “response variation” to address the lack of a response (to an exercise intervention) in a clinical outcome specified a priori. Cardiorespiratory fitness (VO2max) as a clinical exercise response variable has been extensively reviewed; thus, this work focuses on clinical metabolic aspects of

response variation to exercise training in T2D including muscle mitochondrial capacity, insulin sensitivity, glycemic control and metabolic flexibility. Integrated -omics platforms are discussed as an approach to disentangle the complicated relationships between endogenous and exogenous factors that drive response variation to exercise in some individuals. Harnessing the power of combined -omics platforms with deep clinical phenotyping of human study participants will advance the field of exercise metabolism and shift the paradigm—allowing interventions to be targeted to those most likely to benefit and identify novel approaches to treat those who do not.

Nutrient Timing, Nutrient Sensing, and Heterogenity - This talk will focus on nutrient timing and sensing issues. Dr. Peterson will parse nutrient timing into four domains (fasting duration, time of day, regularity, and macronutrient composition) and discuss how each could have an analogous counterpart in exercise. The talk will cover substrate dynamics and molecular pathways influenced by the fasting duration and time of day of eating, including those involved in aging and cancer. Examples will include glycemic and metabolic pathways, the nine hallmarks of aging, and the differential stress sensitization theory. Dr. Peterson will also discuss heterogeneity in the circadian system, substrate oxidation, glycemic rhythms, and lipid rhythms, and the degree to which such heterogeneity may be malleable and/or may influence outcomes. We will also discuss sampling protocols and simple assessments that can be performed, including wearables.

SESSION 3: CIRCADIAN RHYTHMS AND CLOCKS

Exercise Performance and Adaptations - Diurnal differences in endurance exercise performance have been shown in mice and human studies. Most recently, a study using genetic mouse models demonstrated that an intact circadian clock is required for the time of day difference in treadmill performance. In my talk, I will discuss what the circadian clock in muscle does and how clocks could contribute to variability in exercise performance. I will also present data in which we performed treadmill training in mice at either the early part of the active phase (Early runners) or the late part of the active phase (Late runners) and asked about adaptations in performance. We found that the Early runners demonstrated a greater magnitude in running performance compared to the Late runners. Consistent with the time of training we found that the circadian clock mechanism in muscle shifted in phase to more closely align with the time of training. Thus, we suggest that the changing in muscle clock phases likely contribute to the adaptations in endurance exercise performance.

Exercise-Mediated Effects on Skeletal Muscle and Gene Expression - Type 2 diabetes is a life-threatening metabolic disease reaching epidemic proportions, with disease risk scaling linearly due to obesity and inactivity. Disturbed circadian rhythms can cause metabolic dysfunction, highlighting a role of this circuit in type 2 diabetes pathogenesis. Nevertheless, mechanisms underlying disrupted circadian rhythmicity of the intrinsic molecular-clock in type 2 diabetes are unknown. In this lecture, I will cover some of my latest work related to mechanisms by which the timing of food intake or exercise (energetic stressors) interact with peripheral clocks to control metabolic homeostasis. My overarching hypothesis is that synchronizing energetic stressors such as diet and exercise to the molecular circadian clock may maximize the health promoting benefits on glucose and energy metabolism. The goal of my current work is to elucidate the mechanisms by which physiological processes are modulated by the clock

machinery in a diurnal manner including, glucose control, systemic metabolism, and mitochondrial respiration, and how dysregulation of these processes contribute to type 2 diabetes. Molecular mechanisms underpinning the link between peripheral circadian clocks, energy sensing pathways, and the control of glucose homeostasis may one day form the basis of a new class of therapies to prevent insulin resistance.

Reducing Response Heterogeneity of Exercise on Markers of Glucose Homeostasis and Insulin Sensitivity via Timing of Exercise - Exercise training is a cornerstone in the treatment and prevention of type 2 diabetes and a potent way to improve insulin stimulated glucose uptake and glucose homeostasis. Not all individuals, however, benefit to the same extent from the training regimes. We retrospectively ranked obese individuals and patients with type 2 diabetes for their change in insulin stimulated glucose uptake (glucose infusion rate) after a twelve week training intervention (combined aerobic and resistance training). We observed quite a heterogeneous response to the exercise intervention that was not accounted for by differences baseline characteristics, adherence to the training program, changes in markers of mitochondrial density or oxidative capacity. Savikj et al (Diabetologia 2019) observed that following a single and acute exercise session of high-intensity interval training, afternoon training was more efficacious than morning training at improving blood glucose levels in individuals with type 2 diabetes. This prompted us to examine the effect of morning versus afternoon training on the changes in insulin sensitivity and related parameters in obese individuals and patients with type 2 diabetes. We observed that afternoon training was superior to morning training at improving insulin stimulated glucose uptake, markers of adipose tissue insulin sensitivity and changes in body composition. Thus, timing of exercise training is a modifiable determinant of exercise response heterogeneity in glucose homeostasis. The mechanism underlying the beneficial effect of afternoon training vs morning training remains to be elucidated.

SESSION 4: STUDY DESIGN

Optimizing Exercise Training Interventions and Understanding Response Heterogeneity - Multicomponent interventions hold much promise for promotion of physical activity in older adults. Such interventions are typically developed and evaluated using a treatment package approach, in which the intervention is assembled a priori and evaluated by means of a two-group randomized controlled trial (RCT). I will briefly introduce an expanded methodological framework for developing, optimizing, and evaluating behavioral and biobehavioral interventions. This framework, called the multiphase optimization strategy (MOST), is a principled approach that integrates ideas from behavioral science, multivariate statistics, engineering, health economics, and decision science. MOST consists of three phases: preparation, optimization, and evaluation. During the evaluation phase, the investigator conducts an optimization trial using a highly efficient experimental design. The purpose of the optimization trial is to assess the performance of individual intervention components and to determine whether they interact. The results of the optimization trial are used to select components for inclusion in the intervention. Components are selected so as to achieve an optimization objective identified by the investigator. This objective specified the desired balance of effectiveness against affordability, scalability, and efficiency. The objective may be to develop a cost-effective intervention; an intervention that achieves the highest expected level of effectiveness without exceeding an upper limit on implementation costs; the briefest intervention

that achieves a minimum level of effectiveness; or any other reasonable goal. Heterogeneity in response to individual intervention components can be examined by conducting moderation analyses on the data from an optimization trial. The results of these analyses can inform development of adaptive interventions aimed at reducing response heterogeneity by varying intervention approach or dosage strategically according to decision rules and tailoring variables. I propose that MOST offers several benefits, including more rapid long-run improvement of interventions, without requiring a dramatic increase in research resources.

Safe Micro-Randomized Trials - An optimal mHealth strategy for type I diabetes (T1D) maximizes long term patient health by tailoring recommendations for diet, exercise, and insulin uptake to the unique biology and evolving health status of each patient. We develop a response-adaptive randomization method that learns an optimal intervention strategy while controlling the risk of adverse events.

Pooling RCTs to Study Heterogeneous Treatment Effects - Treatment response heterogeneity is commonly defined as non-random variation in the direction or magnitude of a treatment effect for subgroups within a population. This effect is typically observed when treatment effects vary across patients within a clinical trial, which may be a result of individual patient characteristics. However, exploring such effects can be extremely difficult. Most individual randomized controlled trials lack sufficient power to detect subgroup- specific effects. In trials in which subgroup analysis are performed, there is often absence of a priori specification of subgroups to explore, consideration for sample size adequacy for testing the chosen subgroups, and control for type 1 error rate. When an adequate number of studies exists, one approach to overcome sample size limitations for testing heterogeneity within a single study is to pool together multiple data sets that share common treatment groups. In this session, we will discuss the practical and methodological challenges to performing such analyses, approaches for managing these challenges, and examples from the published literature.

Personalized (N-of-1) Trials: The Application of This Trial Design to Understanding Treatment Heterogeneity Response - Personalized (N-of-1) trials are a patient-centered approach and single-case experimental research design that provides essential clinical information for selecting the best treatments for individual patients. In a personalized trial design, individual patients are assessed using multiple crossover trials with continuous objective data collection over alternating time periods of one or more treatments and placebo therapies in randomized blocks. Personalized trials are specifically designed to help patients and their healthcare providers make treatment decisions informed by high-integrity, evidence-based information uniquely relevant to the important outcomes and values. Prior series of personalized trials led participants to changes in exercise, cessation of certain types of exercise, or confirmation of the initial exercise regimen. The randomized crossover design of personalized trials allows the same patient to receive multiple exercise prescriptions while continuously evaluating the effects of each regimen on multiple outcomes. In the case of exercise, these outcomes could include pain, adherence to exercise regimen, and sleep. Once completed, participants can use the information from the personalized trial to identify the exercise regimen that was most effective in improving adherence while minimizing harms. Results from older adults testing yoga will be presented, as the Personalized trial design approach is discussed.

Understanding heterogeneity of exercise response will be illustrated with this trial design approach to testing multiple exercise regimens in older adults.

SESSION 5: BIOMARKERS AND UNDER-RECOGNIZED OUTCOMES

Does Sleep Partly Explain Heterogeneity in the Effects of Exercise on Health? - Significant heterogeneity in the effects of exercise on multiple health-related outcomes is not well-understood. A vast, accumulating literature indicates that poor or inadequate sleep is associated with mortality and multiple morbidities. Differences in sleep could interact with exercise or at least should be considered in epidemiological and experimental studies of exercise and health risk. The effects of exercise on sleep, which can also have a high degree of heterogeneity, could also influence health risks.

Explaining Heterogeneity in the Neurocognitive Consequences of Exercise - Decades of cognitive aging research demonstrate downward trends in nearly all cognitive domains and metrics of brain health. Yet, exercise interventions are effective at improving brain health in late adulthood and observational studies indicate that greater engagement in physical activity is associated with reduced risk of developing dementia. Yet, there remains muddiness and mixed findings in the literature including a poor understanding of the mechanisms that link physical activity to improvements in brain health outcomes in humans and the factors that moderate the effects of exercise on neurocognitive health. That is, while many people engaging in exercise demonstrate significant improvements in brain health over a several month period, others show a more protracted rate of improvement or even negligible changes. The aim of this presentation is not to recapitulate the evidence about the positive effects of exercise on brain health but instead to focus on possible explanations for this heterogeneity of response to exercise treatments on neurocognitive outcomes. I will focus on multiple levels of possible effect moderation including: (a) genetic and molecular factors that might predispose risk for cognitive decline and limit the range of possible improvements, (b) demographic characteristics – e.g., age, sex, that have been shown to influence the magnitude of certain neurocognitive changes from exercise, (c) cognitive and neural baseline characteristics (e.g., low performance at baseline) of the sample that influence the magnitude of benefits over the course of an intervention, (d) environmental factors (e.g., socioeconomic conditions, pollution) that could amplify or mitigate changes in neurocognitive function, (e) the presence of behaviors that also influence cognitive and brain health including intellectual stimulation, sleep, and social interactions. Finally, I will discuss the importance of study design, exercise parameters, and outcome measurements including the selection of neurocognitive instruments and brain regions being studied that are likely to follow different trajectories of change over the course of an intervention. The talk will conclude with a discussion of the gaps in knowledge and several ongoing studies aimed at understanding the mechanisms and moderators of exercise on brain health.

The Gut Microbiota: A Landscape for Improved Understanding of Exercise and Aging Biology - Made up of a diverse consortium of microorganisms, the gut microbiota mediates numerous immune, metabolic, and nervous functions of its host. Accordingly, disturbances to the gut microbiota (i.e., dysbiosis) have been associated with a variety of chronic health conditions across many physiologic systems. More recently, **advanced age has been associated with changes to the gut microbiota** and these changes associate with prevalence of physical frailty

and mortality. These findings highlight a critical need to expand our understanding of the gut microbiota and identify interventions that influence the healthy aging process. **Exercise has the potential to beneficially influence the gut microbiome, but details from humans are sparse and implications are unclear.** *Published and preliminary data from our lab provides early evidence that exercise training does modify the composition and metabolic output of the human gut microbiota***.** This includes changes to bioactive microbial metabolites (i.e., xenometabolites) in previously sedentary middle-aged adults that underwent a 6-week aerobic exercise intervention. Shifts in both fecal and serum xenometabolites paralleled changes in body composition, cardiorespiratory fitness, and markers of insulin sensitivity of the participants, highlighting the possibility that microbial metabolism has a role in mediating exercise adaptations. Importantly, however, we found that microbial composition was highly individualized and that xenometabolic responses to exercise were largely dependent on obesity status. Moreover, serum and fecal xenometabolic responses were not congruent and differed considerably in response to exercise training. These data underscore the need for future microbiome studies that include: (1) larger and more diverse study populations, (2) strong methodological controls such as diet and baseline health status, and (3) multi-tissue analyses of microbial metabolites. This presentation will conclude by discussing recent evidence that describes specific microbial taxa and metabolites that predict a 'healthy aging' process, including walking speed. In turn, we argue that the microbiota and its metabolites should be a part of future studies that aim to understand how exercise modifies healthy aging.